REMARKS

Introductory Comments:

Claims 31-81 and 117-141 are pending and stand variously rejected under 35 U.S.C. §112, first paragraph and 35 U.S.C. §103(a). Applicants respectfully traverse these rejections for reasons discussed below.

Overview of the Above Amendments:

Claims 31, 48 and 56 have been amended in order to recite the subject invention with greater particularity. Specifically, the claims have been amended to make minor wording changes and to correct obvious typographical errors. Additionally, these claims have been amended to delete the homology and percent identity language objected to by the Examiner and to insert the phrase "degenerate variant" which the Examiner acknowledges complies with the written description requirement. (See, page 2 of the Office Action).

Formal Matters:

The Examiner objected to Figures 1-4 and requested applicants insert sequence identification numbers in the blank spaces. Applicants have so done. Marked-up and clean copies of the figures accompany this response. Accordingly, this objection has been overcome.

Rejection of the Claims Under 35 U.S.C. §112, First Paragraph:

Claims 31-33, 48, 56, 64-81 and 117-141 stand rejected under 35 U.S.C. §112, first paragraph. The Action states:

> The written description in this case only sets forth amino acid sequences of various VL and VH regions, some specific nucleotide sequences encoding those sequences and equivalent degenerative codon sequences thereof and therefore the written

> description is not commensurate in scope with the claims drawn to nucleic acid molecules encoding any naturally occurring VH and VL polypeptides which bind to HCV E2.
>
> * * *
>
> [C]laims 31-33, 48, 56 and 64-81 are directed to encompass gene sequences, sequences that hybridize to SEQ ID NO: 15-27, mutated sequences, allelic variants, splice variants, or any nucleotide sequence encoding any antibody variable region which can bind to HCV E2.

Office Action, pages 2-3.

Applicants continue to assert for reasons of record that the previous claims indeed complied with the written description requirement of 35 U.S.C. §112, first paragraph. Nevertheless, independent claims 31, 48 and 56, from which claims 32, 33, 64-81, 117-120 and 126 either directly or ultimately depend, have been amended to delete the terms objected to by the Office. These claims now refer to the specific sequences acknowledged by the Examiner to comply with §112, first paragraph, as well as to degenerate variants of these sequences, also explicitly acknowledged by the Examiner to comply with the written description requirement. See the quote above. Thus, the rejection of at least claims 31-33, 48, 56 and 64-81 has been overcome and withdrawal thereof is respectfully requested.

Applicants note that although claims 117-141 were stated as being rejected, no indication of why these claims, which are already limited to specific sequences, are subject to the rejection. In fact, several of these claims are limited to the exact sequences indicated by the Examiner as complying with 35 U.S.C. §112, first paragraph by the Examiner. In the absence of detailed reasons as to why claims 117-141 were rejected, applicants cannot address the rejection *vis-a-vis* these claims and therefore assume that the inclusion of these claims in the rejection was a typographical error on the part of the Office. Clarification is again requested.

In particular, claims 128-141 recite the sequences of SEQ ID NOS:15-27. The Examiner states at page 3 of the Office Action: "SEQ ID NO: 15-27 meet the written description and enablement provisions of 35 USC 112, first paragraph." Thus, applicants are confused as to why these claims were stated as being rejected. Similarly, claims 117-

127 pertain to embodiments expressly stated by the Office to be adequately described in the application. These claims are framed with reference to amino acid sequences encoded by the nucleotide sequences corresponding to sequences in SEQ ID NOS:15-18 and 22-25 which the Office has stated meet the written description requirement. Applicants, in the previous amendment, queried the Examiner as to why these claims were rejected and asked that if the Patent Office maintain the rejection, the Examiner provide sufficient reasons and, if based on personal knowledge, provide specific data in support thereof in an affidavit pursuant to 37 CFR §1.104(d)(2).

Despite this request, the Examiner has failed to provide evidence or reasons why a person skilled in the art would not recognize a description of the invention defined by these claims in applicants' disclosure. See, e.g., *In re Wertheim,* 191 USPQ 90 (CCPA 1976) (cited in MPEP § 2163.04 in the Examiner Guidelines on Written Description Requirement). Without such reasoning, this rejection must fail. Thus, withdrawal thereof is respectfully requested.

Rejection of the Claims Under 35 U.S.C. §103(a):

The Office rejected claims 31-81 and 117-141 under 35 U.S.C. §103(a), as unpatentable over U.S. Patent No. 5,308,750 to Mehta et al. ("Mehta), in view of U.S. Patent No. 5,919,454 to Brechot et al. ("Brechot") and further in view of Wong et al., *J. Invest. Med.* (1995) 43:397A ("Wong"). The Office acknowledges that Mehta discloses mouse monoclonal antibodies to HCV E2, not human monoclonal antibodies. The Office cites Brechot as allegedly describing human monoclonal antibodies to HCV E1, and F(Ab)2 fragments of these human monoclonal antibodies. The Office acknowledges that Brechot fails to teach polynucleotides encoding human monoclonal F(Ab)2 fragments to HCV E2. Wong is said to provide the motivation to produce recombinant human monoclonal antibodies to HCV E2 based on the disclosure that "antibodies to E2 could block entry of HCV into the cell, and could potentially be used in a therapeutic composition to inhibit HCV infection." Office Action, page 6. However, applicants emphatically disagree that the cited combination renders the claims obvious.

In particular, none of the art cited by the Office pertains to the recombinant

production of human antibodies. In fact, the cited references fail to even discuss in passing that human antibodies could be produced recombinantly. None of Mehta, Brechot or Wong, either alone or in combination, even so much as hints at nucleic acid molecules encoding human Fab molecules as claimed. Protein sequences are not even disclosed for any of the antibodies discussed in the cited art. Moreover, the Office has recognized that nucleic acid molecules as claimed are patentably distinct from recombinant human monoclonal antibodies and single chain antibodies. See, the Restriction Requirement dated November 25, 1997 in this application. Thus, relying on art that may describe embodiments recognized as patentably distinct is wholly improper.

To reiterate, Mehta relates entirely to murine antibodies to putative E2/NS1 proteins of HCV. There is no suggestion in Mehta that human monoclonals to E2 could or should be made. Brechot and Wong do not provide the missing link. As acknowledged by the Office, Brechot does not teach human monoclonal antibodies to HCV E2. Wong is similarly deficient. This brief Abstract deals with murine monoclonal antibodies to HCV E2. There is simply no teaching or suggestion in Wong concerning nucleic acid molecules encoding antibodies that exhibit immunological binding affinity for an HCV E2 antigen. In the absence of any motivation or suggestion regarding the claimed elements, one can only surmise that the Examiner is engaging in improper hindsight reconstruction in making this rejection. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." Moreover, it is also well established that the Examiner may not combine references to create an obviousness rejection unless there is some suggestion or motivation in the prior art to make the combination. *See, e.g., Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 43 USPQ2d 1294 (Fed. Cir. 1997).

Applicants submit, based on the foregoing discussion, that a *prima facie* case of obviousness has not been presented by the Office. Accordingly, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further written communications regarding this application to:

Alisa Harbin, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

Respectfully submitted,
COOLEY GODWARD LLP

Date: 2/11/03

By: _____
Roberta L. Robins
Reg. No. 33,208

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Tel: (650) 843-5000
Fax: (650) 857-0663

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 31, 48 and 56 have been amended as follows:

31. (Three times amended) An isolated nucleic acid molecule encoding a human Fab molecule, [comprising] wherein the nucleic acid molecule comprises:

a first nucleotide sequence encoding a first polypeptide that is [homologous to the] a binding portion of a **γ1** heavy chain variable region (V_H) of said human Fab molecule where said heavy chain region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen; and wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 4A (SEQ ID NO:22) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4B (SEQ ID NO:23) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4C (SEQ ID NO:24) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4D (SEQ ID NO:25) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4E (SEQ ID NO:19) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4F (SEQ ID NO:26) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 4G (SEQ ID NO:27) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; and

a second nucleotide sequence encoding a second polypeptide that is [homologous to the] a binding portion of a **κ** light chain variable region (V_L) of said human Fab

molecule where said light chain variable region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen, and wherein the second nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 3A (SEQ ID NO:15) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3B (SEQ ID NO:16) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3C (SEQ ID NO:17) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3D (SEQ ID NO:18) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3E (SEQ ID NO:19) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3F (SEQ ID NO:20) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 3G (SEQ ID NO:21) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof, and wherein said Fab molecules have binding affinity greater than 1×10^7 M^{-1} for HCV E2.

48. (Three times amended) An isolated nucleic acid molecule, comprising a first nucleotide sequence encoding a binding portion of a **γ1** heavy chain variable region (V_H) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 4A (SEQ ID NO:22) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4B (SEQ ID NO:23) or a [contiguous sequence of nucleotides with at

least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4C (SEQ ID NO:24) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4D (SEQ ID NO:25) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4E (SEQ ID NO:19) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4F (SEQ ID NO:26) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 4G (SEQ ID NO:27) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof.

56. (Three times amended) An isolated nucleic acid molecule, comprising a first nucleotide sequence encoding a binding portion of a κ light chain variable region (V_L) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 3A (SEQ ID NO:15) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3B (SEQ ID NO:16) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3C (SEQ ID NO:17) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3D (SEQ ID NO:18) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3E (SEQ ID NO:19) or a [contiguous sequence of nucleotides with at least 90% sequence

identity thereto] degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3F (SEQ ID NO:20) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 3G (SEQ ID NO:21) or a [contiguous sequence of nucleotides with at least 90% sequence identity thereto] degenerate variant thereof.

In the Drawings:

Figures 1-4 have been amended as shown in red ink.

Currently Pending Claims

31. (Three times amended) An isolated nucleic acid molecule encoding a human Fab molecule, wherein the nucleic acid molecule comprises:

a first nucleotide sequence encoding a first polypeptide that is a binding portion of a **γ1** heavy chain variable region (V_H) of said human Fab molecule where said heavy chain region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen; and wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 4A (SEQ ID NO:22) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4B (SEQ ID NO:23) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4C (SEQ ID NO:24) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4D (SEQ ID NO:25) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4E (SEQ ID NO:19) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4F (SEQ ID NO:26) or a degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 4G (SEQ ID NO:27) or a degenerate variant thereof; and

a second nucleotide sequence encoding a second polypeptide that is a binding portion of a **κ** light chain variable region (V_L) of said human Fab molecule where said light chain variable region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen, and wherein the second nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 3A (SEQ ID NO:15) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3B (SEQ ID NO:16) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3C (SEQ ID NO:17) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3D (SEQ ID NO:18) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3E (SEQ ID NO:19) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3F (SEQ ID NO:20) or a degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 3G (SEQ ID NO:21) or a

degenerate variant thereof, and wherein said Fab molecules have binding affinity greater than 1 x 10^7 M^{-1} for HCV E2.

32. The nucleic acid molecule of claim 31, further comprising:

a third nucleotide sequence encoding a first leader sequence peptide, wherein said third nucleotide sequence is operably linked to the 5' terminus of the first nucleotide sequence and is capable of causing secretion of the encoded heavy chain variable region when the encoded heavy chain variable region and the first leader sequence peptide are expressed; and

a fourth nucleotide sequence encoding a second leader sequence peptide, wherein said fourth nucleotide sequence is operably linked to the 5' terminus of the second nucleotide sequence and is capable of causing secretion of the encoded light chain variable region when the encoded light chain variable region and the second leader sequence peptide are expressed.

33. The nucleic acid molecule of claim 32, wherein the third and fourth nucleotide sequences are selected from the group of leader sequences consisting of *omp* A and *pel*B.

34. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4A (SEQ ID NO:22).

35. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4B (SEQ ID NO:23).

36. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4C (SEQ ID NO:24).

37. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4D (SEQ ID NO:25).

38. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4E (SEQ ID NO:19).

39. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4F (SEQ ID NO:26).

40. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4G (SEQ ID NO:27).

41. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3A (SEQ ID NO:15).

42. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3B (SEQ ID NO:16).

43. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3C (SEQ ID NO:17).

44. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3D (SEQ ID NO:18).

45. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted Figure 3E (SEQ ID NO:19).

46. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3F (SEQ ID NO:20).

47. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3G (SEQ ID NO:21).

48. (Three times amended) An isolated nucleic acid molecule, comprising a first nucleotide sequence encoding a binding portion of a γ1 heavy chain variable region (V_H) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 4A (SEQ ID NO:22) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4B (SEQ ID NO:23) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4C (SEQ ID NO:24) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4D (SEQ ID NO:25) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4E (SEQ ID NO:19) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 4F (SEQ ID NO:26) or a degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 4G (SEQ ID NO:27) or a degenerate variant thereof.

49. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4A (SEQ ID NO:22).

50. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4B (SEQ ID NO:23).

51. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4C (SEQ ID NO:24).

52. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4D (SEQ ID NO:25).

53. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4E (SEQ ID NO:19).

54. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4F (SEQ ID NO:26).

55. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4G (SEQ ID NO:27).

56. (Three times amended) An isolated nucleic acid molecule, comprising a first nucleotide sequence encoding a binding portion of a κ light chain variable region (V_L) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of nucleotides depicted in Figure 3A (SEQ ID NO:15) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3B (SEQ ID NO:16) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3C (SEQ ID NO:17) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3D (SEQ ID NO:18) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3E (SEQ ID NO:19) or a degenerate variant thereof; the contiguous sequence of nucleotides depicted in Figure 3F (SEQ ID NO:20) or a degenerate variant thereof; and the contiguous sequence of nucleotides depicted in Figure 3G (SEQ ID NO:21) or a degenerate variant thereof.

57. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence depicted in Figure 3A (SEQ ID NO:15).

58. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3B (SEQ ID NO:16).

59. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3C (SEQ ID NO:17).

60. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3D (SEQ ID NO:18).

61. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3E (SEQ ID NO:19).

62. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3F (SEQ ID NO:20).

63. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3G (SEQ ID NO:21).

64. An expression vector, comprising the nucleic acid molecule of claim 31 operably linked to control sequences that direct the transcription of the first and second nucleotide sequences whereby said first and second nucleotide sequences can be transcribed and translated in a host cell.

65. The expression vector of claim 64, wherein the control sequences are capable of directing the transcription of the first and second nucleotide sequences in a prokaryotic host cell.

66. The expression vector of claim 64, wherein the control sequences are capable of directing the transcription of the first and second nucleotide sequences in a eukaryotic host cell.

67. An expression vector, comprising the nucleic acid molecule of claim 48 operably linked to control sequences that direct the transcription of the first nucleotide sequence whereby said first nucleotide sequence can be transcribed and translated in a host cell.

68. The expression vector of claim 67, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a prokaryotic host cell.

69. The expression vector of claim 67, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a eukaryotic host cell.

70. An expression vector, comprising the nucleic acid molecule of claim 56 operably linked to control sequences that direct the transcription of the first nucleotide sequence whereby said first nucleotide sequence can be transcribed and translated in a host cell.

71. The expression vector of claim 70, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a prokaryotic host cell.

72. The expression vector of claim 70, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a eukaryotic host cell.

73. A prokaryotic host cell transformed with the expression vector of claim 65.

74. A prokaryotic host cell transformed with the expression vector of claim 68.

75. A prokaryotic host cell transformed with the expression vector of claim 71.

76. A eukaryotic host cell transformed with the expression vector of claim 66.

77. A eukaryotic host cell transformed with the expression vector of claim 68.

78. A eukaryotic host cell transformed with the expression vector of claim 72.

79. A method of producing a recombinant human Fab molecule, comprising:
(a) providing a population of transformed host cells according to claim 76; and
(b) expressing said recombinant Fab molecule from the expression vector.

80. A method of producing a recombinant polypeptide having a binding portion of a **γ1** heavy chain variable region (V_H) of a human Fab molecule, comprising:

(a) providing a population of transformed host cells according to claim 77; and

(b) expressing said recombinant polypeptide from the expression vector.

81. A method of producing a recombinant polypeptide having a binding portion of a **κ** light chain variable region (V_L) of a human Fab molecule, comprising:

(a) providing a population of transformed host cells according to claim 78; and

(b) expressing said recombinant polypeptide from the expression vector.

117. The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1A (SEQ ID NO: 1) and the contiguous sequence of amino acids depicted in Figure 2A (SEQ ID NO: 5).

118. The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1B (SEQ ID NO: 2) and the contiguous sequence of amino acids depicted in Figure 2B (SEQ ID NO: 6).

119. The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1C (SEQ ID NO: 3) and the contiguous sequence of amino acids depicted in Figure 2C (SEQ ID NO: 7).

120. The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1D (SEQ ID NO: 4) and the contiguous sequence of amino acids depicted in Figure 2D (SEQ ID NO: 8).

121. An isolated nucleic acid molecule that encodes a recombinant human monoclonal antibody that exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen, wherein the antibody comprises at least one group of three complementarity determining regions (CDRs) interposed between framework regions (FRs) said FRs derived from a human immunoglobulin, wherein the group of three CDRs is selected from the group consisting of amino acid residue numbers 32-36, 51-71, 104-121 of SEQ ID NO:1; amino acid residue numbers 32-36, 51-67, 100-116 of SEQ ID NO:2; amino acid residue numbers 32-36, 51-67, 100-117 of SEQ ID NO:3; amino acid residue numbers 31-35, 50-66, 99-114 of SEQ ID NO:4; amino acid residue numbers 23-34, 49-56, 89-97 of SEQ ID NO:5; amino acid residue numbers 23-33, 49-55, 88-95 of SEQ ID NO:6; amino acid residue numbers 23-34, 50-56, 89-97 of SEQ ID NO:7; and amino acid residue numbers 23-33, 49-55, 88-96 of SEQ ID NO:8.

122. The isolated nucleic acid molecule of claim 121, wherein the antibody encoded by the nucleic acid molecule comprises a first group of CDRs with amino acid residue numbers 32-36, 51-71, 104-121 of SEQ ID NO:1 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-34, 49-56, 89-97 of SEQ ID NO:5, interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

123. The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers 32-36, 51-67, 100-116 of SEQ ID NO:2 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-33, 49-55, 88-95 of SEQ ID NO:6, interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

124. The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers 32-36, 51-67, 100-117 of SEQ ID NO:3 interposed between FRs, and a second group of CDRs with amino acid residue numbers amino acid residue numbers 23-34, 50-56, 89-97 of SEQ ID NO:7

interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

125. The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers amino acid residue numbers 31-35, 50-66, 99-114 of SEQ ID NO:4 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-33, 49-55, 88-96 of SEQ ID NO:8 interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

126. A method for providing an antibody titer to HCV in a mammalian subject, comprising introducing a therapeutically effective amount of the composition comprising the isolated nucleic acid of claim 120 to said subject.

127. A method for providing an antibody titer to HCV in a mammalian subject, comprising introducing a therapeutically effective amount of the vaccine composition of claim 121 to said subject.

128. (New) An isolated nucleic acid molecule encoding a human Fab molecule, wherein the nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, and SEQ ID NO:27.

129. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:15.

130. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:16.

131. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:17.

132. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:18.

133. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:19.

134. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:20.

135. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:21.

136. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:22.

137. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:23.

138. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:24.

139. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:25.

140. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:26.

141. (New) The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:27.